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Introduction: ADHD Genetics and Heritability

ADHD has very high heritability (60-90% from twin studies) but individual genetic variants have small effects, requiring analysis of thousands of variants together. The disorder involves multiple neurotransmitter systems beyond just dopamine, including serotonin, acetylcholine, and genes affecting brain development and connectivity. (5 sources)

Attention-deficit/hyperactivity disorder (ADHD) represents one of the most heritable psychiatric conditions, with twin studies consistently demonstrating heritability estimates ranging from 60% to 90% (Quintero et al., 2022) (Curatolo et al., 2010). More recent estimates using genetic data suggest that genetic factors contribute approximately 74% to the overall risk of developing ADHD (Poddar et al., 2025). However, this high heritability contrasts sharply with the modest effects of individual genetic variants, as single-nucleotide polymorphism (SNP) analysis has estimated SNP-based heritability between only 10% and 28% (Quintero et al., 2022).

This apparent paradox reflects the highly polygenic nature of ADHD, where large-scale genome-wide association studies (GWAS) have identified over 7,300 genetic variants that increase risk (Poddar et al., 2025). The overall effect size of individual variants is small, and much of the genetic risk arises from the cumulative influence of multiple small-risk variants, as indicated by polygenic risk scores (Poddar et al., 2025). Candidate gene studies have identified notable polymorphisms in genes affecting multiple neurotransmitter systems, with DRD4 and SNAP25 showing strong links to ADHD in over 70% of studies, while DRD5 and SLC6A3 were associated in 60% of studies (Poddar et al., 2025).

The genetic architecture of ADHD extends well beyond the traditionally emphasized dopaminergic system. GWAS findings indicate genes involved in neuronal plasticity mechanisms including neuronal migration, cell adhesion, and neuron proliferation, as well as genes affecting the synthesis or release of multiple neurotransmitters including dopamine, serotonin, and norepinephrine (Quintero et al., 2022). Additionally, ADHD-associated mutations encompass physiological processes including circadian rhythm mechanisms, and rare copy number variants affecting glutamatergic and cholinergic pathways, such as duplications in the CHRNA7 gene (Quintero et al., 2022) (Poddar et al., 2025) (Williams et al., 2012) (Akutagava-Martins et al., 2014). This genetic complexity suggests that effective multi-SNP profiling for ADHD must account for variants across diverse biological pathways rather than focusing solely on dopaminergic function.

Evidence

(Quintero et al., 2022)

Molecular Characterisation of the Mechanism of Action of Stimulant Drugs Lisdexamfetamine and Methylphenidate on ADHD

Neurobiology: A Review

"Genetics has a great weight in ADHD, with a heritability ranging from 60% to 90% according to several studies carried out in twins (Curatolo et al., 2010)(Coghill et al., 2009). However, other studies using single-nucleotide polymorphism (SNP) analysis have estimated that SNP-based heritability ranged between 10% and 28% (Lee et al., 2013)"

"Genome-wide association studies (GWAS) have indicated genes playing a role in ADHD that could be linked to neuronal plasticity mechanisms (neuronal migration, cell adhesion and neuron proliferation) (Ribasés et al., 2011) or to deficiencies in the synthesis or release of neurotransmitters (NTs), mainly DA, but also serotonin and NE (Coghill et al., 2009)[62]. However, ADHDassociated mutations have been reported to include a wide range of different physiological processes including circadian rhythm mechanisms (Bijlenga et al., 2019)."

(Curatolo et al., 2010)

The neurobiological basis of ADHD

"Attention-Deficit/Hyperactivity Disorder is not a single pathophysiological entity and appears to have a complex etiology. There are multiple genetic and environmental risk factors with small individual effect that act in concert to create a spectrum of neurobiological liability. Structural imaging studies show that brains of children with Attention-Deficit/Hyperactivity Disorder are significantly smaller than unaffected controls. The prefrontal cortex, basal ganglia and cerebellum are differentially affected and evidence indicating reduced connectivity in white matter tracts in key brain areas is emerging. Genetic, pharmacological, imaging, and animal models highlight the important role of dopamine dysregulation in the neurobiology of Attention-Deficit/Hyperactivity Disorder. To date, stimulants are the most effective psychopharmacological treatments available for Attention-Deficit/Hyperactivity Disorder. Currently only immediate release methylphenidate and atomoxetine are approved for the treatment of ADHD in Italy. Drug treatment should always be part of a comprehensive plan that includes psychosocial, behavioural and educational advice and interventions."

(Poddar et al., 2025)

Unraveling Attention-Deficit/Hyperactivity Disorder Etiology: Current Challenges and Future Directions in Treatment

"ADHD has a strong heritable component, with genetic factors contributing approximately 74% to the overall risk of developing the disorder"

"large-scale genome-wide association studies (GWAS) have identified over 7300 genetic variants that increase risk, underscoring the polygenic nature of ADHD"

"Key genes involved in dopamine regulation, such as DRD4 and DAT1, have emerged as central players in the genetic architecture of ADHD"

"Candidate gene studies have identified significant polymorphisms in genes like SLC6A3 (dopamine transporter) [41], DRD4 and DRD5 (dopamine receptors) (Swanson et al., 1998)[43], SLC6A4 (serotonin transporter), HTR1B (serotonin receptor), and SNAP25 (synaptosome protein). Both DRD4 and SNAP25 have shown strong links to ADHD (Taylor et al., 2023), each being associated in over 70% of studies, while DRD5 and SLC6A3 [43] were associated in 60% of studies"

"the overall effect size of individual variants is small, and much of the genetic risk is believed to arise from the cumulative influence of multiple small-risk variants, as indicated by polygenic risk scores (PRSs)"

"The polygenic nature of ADHD is evident from GWAS findings, as multiple genes, including those involved in dopamine regulation (DUSP6) and neuronal wiring (SEMA6D), contribute to the overall genetic susceptibility [65]"

"duplications in the CHRNA7 gene, which modulates dopaminergic neurons, highlight the importance of glutamatergic and cholinergic pathways in ADHD's pathophysiology (Williams et al., 2012)(Akutagava-Martins et al., 2014)(Mick et al., 2008)(Carrey et al., 2007)."

(Williams et al., 2012)

Genome-Wide Analysis of Copy Number Variants in Attention Deficit Hyperactivity Disorder: The Role of Rare Variants and Duplications at 15q13.3

"Objective: Attention deficit hyperactivity disorder (ADHD) is a common, highly heritable psychiatric disorder. Because of its multifactorial etiology, however, identifying the genes involved has been difficult. The authors followed up on recent findings suggesting that rare copy number variants (CNVs) may be important for ADHD etiology. Method: The authors performed a genome-wide analysis of large, rare CNVs (<1% population frequency) in children with ADHD (N=896) and comparison subjects (N=2,455) from the IMAGE II Consortium. Results: The authors observed 1,562 individually rare CNVs >100 kb in size, which segregated into 912 independent loci. Overall, the rate of rare CNVs >100 kb was 1.15 times higher in ADHD case subjects relative to comparison subjects, with duplications spanning known genes showing a 1.2-fold enrichment. In accordance with a previous study, rare CNVs >500 kb showed the greatest enrichment (1.28-fold). CNVs identified in ADHD case subjects were significantly enriched for loci implicated in autism and in schizophrenia. Duplications spanning the CHRNA7 gene at chromosome 15q13.3 were associated with

ADHD in single-locus analysis. This finding was consistently replicated in an additional 2,242 ADHD case subjects and 8,552 comparison subjects from four independent cohorts from the United Kingdom, the United States, and Canada. Presence of the duplication at 15q13.3 appeared to be associated with comorbid conduct disorder. Conclusions: These findings support the enrichment of large, rare CNVs in ADHD and implicate duplications at 15q13.3 as a novel risk factor for ADHD. With a frequency of 0.6% in the populations investigated and a relatively large effect size (odds ratio=2.22, 95% confidence interval=1.5–3.6), this locus could be an important contributor to ADHD etiology."

(Akutagava-Martins et al., 2014)

Glutamatergic copy number variants and their role in attention-deficit/hyperactivity disorder

"Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder with a strong genetic component. The glutamate metabotropic receptor genes (GRMs) have been considered potential candidates for ADHD susceptibility. The aim of the present study was to investigate if copy number variants (CNVs) in GRM1, GRM5, and GRM8 genes are overrepresented in ADHD subjects. A total of 1038 individuals with ADHD and 1057 subjects without this disorder were investigated. No significant difference in the total number of CNVs was found comparing the entire ADHD sample and the population sample without ADHD (P = 0.326, OR = 1.112, 95% CI = 0.762–1.624). The presence of CNVs was associated with lower intelligence quotient (IQ) scores in ADHD samples (P = 0.026, OR = 1.824, 95% CI = 1.066–3.121) but not in the sample of individuals without ADHD. CNVs in GRM5 were associated with presence of anxiety disorders in ADHD cases (P = 0.002, OR = 3.915, 95% CI = 1.631–9.402), but not in individuals without ADHD. Taken together, our results suggest a role for glutamate in ADHD as CNVs in the glutamatergic genes investigated herein were associated with cognitive and clinical characteristics of ADHD individuals. © 2014 The Authors. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics Published by Wiley Periodicals, Inc."

Dopaminergic System SNPs

The dopamine system is central to ADHD genetics, with key variants in receptor genes (DRD4, DRD2) and the dopamine transporter (DAT1/SLC6A3) affecting brain function and behavior. The DRD4 gene shows particularly strong associations, with the 7-repeat allele and the -521 C/T polymorphism both linked to increased ADHD risk through reduced dopamine signaling. (7 sources)

The dopaminergic system represents the most extensively studied neurotransmitter pathway in ADHD genetics, with multiple genes showing consistent associations across candidate gene studies. Dopamine receptors D1 and D2 are abundant in brain regions involved in reward circuits, learning and memory, and locomotor activity, while patients with ADHD show higher density of the dopamine transporter (DAT), which could lead to altered dopamine levels in the synaptic cleft (Silva et al., 2023).

The DRD4 gene has emerged as one of the most robust genetic markers for ADHD susceptibility. The 7-repeat allele of DRD4 increases susceptibility to ADHD and has been connected to modifications in dopamine pathway functioning that can contribute to disruptions in neural communication and difficulties in cognitive regulation and behavioral control (Jagani et al., 2023) (Zhang et al., 2011). Additionally, the DRD4 -521 C/T single-nucleotide polymorphism shows significant functional consequences, with the T allele displaying 40% lower transcriptional activity than the C allele and occurring at statistically significantly higher frequencies in children with ADHD compared to neurotypical controls (Zhang et al., 2022).

Candidate gene studies have consistently identified key dopaminergic variants, with both DRD4 and the dopamine transporter gene SLC6A3 (also known as DAT1) showing strong associations with ADHD (Poddar et al., 2025). The dopamine receptor genes DRD4 and DRD5, along with SLC6A3, have been associated with ADHD in 60-70% of studies, making them among the most replicated genetic findings in ADHD research (Poddar et al., 2025). Treatment response studies have further supported the clinical relevance of dopaminergic variants, as ADHD medication responses appear to be regulated by genes in the dopamine pathway including DRD4 and SLC6A3, as well as COMT which affects catecholamine metabolism (Zhao et al., 2025).

The dopaminergic pathway remains crucial in ADHD pathogenesis and can be affected by environmental factors and interactions with other neurotransmitter pathways (Kessi et al., 2022). Epigenetic modifications including SUMOylation, methylation, and acetylation have been reported in dopaminergic pathway genes, suggesting additional layers of regulatory complexity beyond simple genetic variants (Kessi et al., 2022).

Evidence

(Silva et al., 2023)

An overview on neurobiology and therapeutics of attention-deficit/hyperactivity disorder

"The physiological changes induced by the binding of dopamine and norepinephrine to their respective receptors involve the modulation of several cognitive and executive processes usually impaired in ADHD (see Table 1), corroborating the monoaminergic hypothesis for ADHD pathophysiology (Campo et al., 2011). For example, dopamine receptors of subtypes D1 and D2 are abundant in brain regions mainly involved in signaling reward circuits, learning and memory, and locomotor activity (Beaulieu et al., 2011). Also, patients with ADHD have a higher density of the dopamine transporter (DAT), responsible for the reuptake of DA into presynaptic neurons (Fusar-Poli et al., 2012), which could lead to alterations in dopamine levels in the synaptic cleft. The binding of norepinephrine with adrenergic receptors has been shown to modulate working memory processes, for which moderate or high levels of this neurotransmitter present differential binding affinities to each type of receptor and consequently different physiological effects on working memory (Berridge et al., 2016). Furthermore, the effects of methylphenidate treatment on working memory appear to be dependent on α2 noradrenergic receptors, whereas the improvement in sustained attention involves the α1 subtype [94]."

(Jagani et al., 2023)

Innovative Approaches to Detecting Neurodevelopmental Disorders

"Research has shown that individuals carrying the 7-repeat allele of the DRD4 gene are more susceptible to ADHD [61](Zhang et al., 2011). This genetic marker has been connected to modifications in the functioning of dopamine pathways within the brain. These alterations can contribute to disruptions in neural communication, potentially leading to challenges in cognitive regulation and behavioral control. Consequently, these changes in dopamine-related pathways could play a role in the development of conditions like ADHD, where difficulties extend beyond just attention and impulsivity and encompass broader cognitive and behavioral aspects"

"copy number variations (CNVs), singlenucleotide polymorphisms (SNPs), and microdeletions/microduplications. CNVs and SNPs have been associated with various intellectual disabilities (Kessi et al., 2018)."

(Zhang et al., 2011)

ADHDgene: a genetic database for attention deficit hyperactivity disorder

"With a worldwide prevalence of ~5%,attention deficit hyperactivity disorder (ADHD) has become one of the most common psychiatric disorders. The polygenetic nature of ADHD indicates that multiple genes jointly contribute to the development of this complex disease. Studies aiming to explore genetic susceptibility of ADHD have been increasing in recent years. There is a growing need to integrate the genetic data from various genetic studies to provide a comprehensive data set and uniform access for convenience of in-depth data mining. So far, there has been no such effort for ADHD. To address the genetic complexity of ADHD, we developed the ADHDgene database by integrating ADHD-related genetic factors by profound literature reading. Based on the data from the literature, extended functional analysis, including linkage disequilibrium analysis, pathway-based analysis and gene mapping were performed to provide new insights into genetic causes of ADHD. Moreover, powerful search tools and a graphical browser were developed to facilitate the navigation of the data and data connections. As the first genetic database for ADHD, ADHDgene aims to provide researchers with a central genetic resource and analysis platform for ADHD and is freely available at http://adhd.psych.ac.cn/."

(Zhang et al., 2022)

Effects of the DRD4 −521 C/T SNP on Local Neural Activity and Functional Connectivity in Children With ADHD

"The present study aimed to investigate the effects of the dopamine receptor D4 (DRD4) −521 C/T single-nucleotide polymorphism on brain function among children with attention deficit hyperactivity disorder (ADHD) and to evaluate whether brain function is associated with behavioral performance among this demographic"

"A previous study reported that the transcriptional activity for the T allele in the DRD4 −521 C/T SNP was 40% lower than that of the C allele (16). Additionally, a case-control study found that the frequency of the T allele in children with ADHD was statistically significantly higher than that of the C allele, while the frequencies of the C and T alleles in the children's neurotypical counterparts were similar (Yang et al., 2008). Therefore, based on findings within the literature to date, the T allele is considered a risk gene for ADHD"

"Moreover, the DRD4 −521 C/T SNP has been confirmed to be a critical factor in the pathogenesis of ADHD (Yang et al., 2008)(Das et al., 2011)22)."

(Poddar et al., 2025)

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"ADHD has a strong heritable component, with genetic factors contributing approximately 74% to the overall risk of developing the

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(Zhao et al., 2025)

Genome data based deep learning identified new genes predicting pharmacological treatment response of attention deficit hyperactivity disorder

"The current GWAS results identified two significant loci (rs10880574, P = 2.39E-09; rs2000900, P = 3.31E-09) which implicated two genes, TMEM117 and MYO5B, that were primarily associated with both brain- and gut-related disorders"

"Notably, the variant that contributed most to the CNN model was NKAIN2, an ADHD-related gene, which is also associated with metabolic processes"

"Previous candidate gene-based studies showed that ADHD treatment responses were probably regulated by genes involved in neurotransmitter system (Myer et al., 2018), including dopamine pathway (DRD4, SLC6A3), norepinephrine pathway (SLC6A2, ADRA2A), and catecholamines metabolism (COMT); and cytochrome P450 isoenzyme [8](Trzepacz et al., 2008), including CYP2D6 and CES1."

(Kessi et al., 2022)

Attention-deficit/hyperactive disorder updates

"Several genes have been reported to associate with ADHD: DRD1, DRD2, DRD4, DAT1, TPH2, HTR1A, HTR1B, SLC6A4, HTR2A, DBH, NET1, ADRA2A, ADRA2C, CHRNA4, CHRNA7, GAD1, GRM1, GRM5, GRM7, GRM8, TARBP1, ADGRL3, FGF1, MAOA, BDNF, SNAP25, STX1A, ATXN7, and SORCS2"

"The majority of the available animal models are related to the dopaminergic pathway. Epigenetic changes including SUMOylation, methylation, and acetylation have been reported in genes related to the dopaminergic pathway"

"The dopaminergic pathway remains to be crucial in the pathogenesis of ADHD. It can be affected by environmental factors and other pathways."

Serotonergic System SNPs

Serotonin system genes, particularly TPH2 (affecting serotonin synthesis) and 5-HT receptor variants, show significant associations with ADHD symptoms and brain function. These serotonergic effects may interact with dopamine systems, suggesting that ADHD involves complex cross-talk between multiple neurotransmitter pathways. (4 sources)

The serotonergic system represents an important but less studied component of ADHD genetics, with genetic association studies identifying serotonergic system gene variants associated with ADHD phenotype (Akhrif et al., 2023). Serotonergic neurotransmission plays an important role in ADHD, as genetic variations in these genes affect both impulsive behavior and neural functioning at rest and under task conditions (Akhrif et al., 2023) (Oades et al., 2008).

Tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme in brain serotonin synthesis, has shown

particularly notable associations with ADHD. The TPH2 G-703T (rs4570625) polymorphism influences response control and prefrontal signaling in ADHD patients, with both genotype and DNA methylation in the 5' untranslated region associated with altered brain activity in fronto-parietal regions and behavioral performance (Akhrif et al., 2023). Patients carrying the T allele show the highest wavelet variance and longest reaction times, indicating a gene-dosage effect where the phenotype results from cumulative effects of ADHD and TPH2 variation (Akhrif et al., 2023).

Serotonin receptor variants also contribute to ADHD risk and symptom severity. The 5-HT1B receptor SNP rs6296 has been significantly associated with high scores on the Adult ADHD Self-Report Scale, specifically in the inattentive domain (Jackson et al., 2025). Preclinical studies support this association, as 5-HT1B receptor knockouts show increased hyperactivity and impulsivity, with impulsivity being improved when receptors are restored in adulthood (Jackson et al., 2025). The serotonin transporter polymorphism 5-HTTLPR also moderates the relationship between stress exposure and ADHD severity, with S-allele carriers showing different stress-related connectivity patterns in executive control and default mode networks (Meer et al., 2016).

Importantly, serotonergic transmission changes are linked to alterations in dopaminergic transmission, as dopamine release in several brain regions is modulated by 5-HT receptor activity (Jackson et al., 2025). This suggests that serotonin and dopamine changes observed in ADHD may be interconnected rather than independent pathways (Jackson et al., 2025). Family-based association studies have identified both separate and overlapping genetic influences on different types of impulsivity, with serotonergic mechanisms showing wider ranges of small-effect variants potentially influencing cognitive impulsivity compared to aggressive impulsivity (Oades et al., 2008).

Evidence

(Akhrif et al., 2023)

Serotonergic modulation of normal and abnormal brain dynamics: The genetic influence of the TPH2 G-703T genotype and DNA methylation on wavelet variance in children and adolescents with and without ADHD

"Tryptophan hydroxylase 2 (TPH2) is the rate-limiting enzyme in brain serotonin synthesis. The TPH2 gene has frequently been investigated in relation to ADHD, e.g., showing that TPH2 G-703T (rs4570625) polymorphism influences response control and prefrontal signaling in ADHD patients"

"Both, TPH2 G-703T (rs4570625) genotype and DNA methylation in the 5' untranslated region (5'UTR) of TPH2 were associated with wavelet variance in fronto-parietal regions and behavioral performance, taking TPH2 genotype into account"

"comparisons between genotypes of patients and controls revealed highest wavelet variance and longest reaction times in patients carrying the T allele [indicative for a gene-dosage effect, i.e., the WI phenotype is a direct result of the cumulative effect of ADHD and TPH2 variation]"

"serotoninergic neurotransmission seems to play an important role in ADHD as genetic association studies identified serotonergic system gene variants to be associated with ADHD phenotype (266046195)(Rooij et al., 2015)"

"in patients with ADHD impulsive behavior (Stoltenberg et al., 2012) as well as neural functioning at rest and under task varied between genotypes of serotonergic genes (Meer et al., 2016)"

(Oades et al., 2008)

The influence of serotonin- and other genes on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/hyperactivity disorder (ADHD): Findings from a family-based association test (FBAT) analysis

"BackgroundLow serotonergic (5-HT) activity correlates with increased impulsive-aggressive behavior, while the opposite association may apply to cognitive impulsiveness. Both types of impulsivity are associated with attention-deficit/hyperactivity disorder (ADHD), and genes of functional significance for the 5-HT system are implicated in this disorder. Here we demonstrate the separation of aggressive and cognitive components of impulsivity from symptom ratings and test their association with 5-HT and functionally related genes using a family-based association test (FBAT-PC).MethodsOur sample consisted of 1180 offspring from 607 families from the International Multicenter ADHD Genetics (IMAGE) study. Impulsive symptoms were assessed using the long forms of the Conners and the Strengths and Difficulties parent and teacher questionnaires. Factor analysis showed that the symptoms aggregated into parent- and teacher-rated behavioral and cognitive impulsivity. We then selected 582 single nucleotide

polymorphisms (SNPs) from 14 genes directly or indirectly related to 5-HT function. Associations between these SNPs and the behavioral/cognitive groupings of impulsive symptoms were evaluated using the FBAT-PC approach.ResultsIn the FBAT-PC analysis for cognitive impulsivity 2 SNPs from the gene encoding phenylethanolamine N-methyltransferase (PNMT, the rate-limiting enzyme for adrenalin synthesis) attained corrected gene-wide significance. Nominal significance was shown for 12 SNPs from BDNF, DRD1, HTR1E, HTR2A, HTR3B, DAT1/SLC6A3, and TPH2 genes replicating reported associations with ADHD. For overt aggressive impulsivity nominal significance was shown for 6 SNPs from BDNF, DRD4, HTR1E, PNMT, and TPH2 genes that have also been reported to be associated with ADHD. Associations for cognitive impulsivity with a SERT/SLC6A4 variant (STin2: 12 repeats) and aggressive behavioral impulsivity with a DRD4 variant (exon 3: 3 repeats) are also described.DiscussionA genetic influence on monoaminergic involvement in impulsivity shown by children with ADHD was found. There were trends for separate and overlapping influences on impulsive-aggressive behavior and cognitive impulsivity, where an association with PNMT (and arousal mechanisms affected by its activity) was more clearly involved in the latter. Serotonergic and dopaminergic mechanisms were implicated in both forms of impulsivity with a wider range of serotonergic mechanisms (each with a small effect) potentially influencing cognitive impulsivity. These preliminary results should be followed up with an examination of environmental influences and associations with performance on tests of impulsivity in the laboratory."

(Jackson et al., 2025)

Serotonin dysfunction in ADHD

"5-HT 1b receptor SNP rs6296 has also been found to be significantly associated with high scores on the Adult ADHD Self-Report Scale (ASRS), specifically in the inattentive domain, in a candidate gene study with a moderate sample size (N = 990) (Bidwell et al., 2017). Although genetically complex, it is evident that genetic changes to serotonergic neurotransmission are implicated in at least some cases of ADHD"

"Preclinical work in rodents has found knockouts for the 5-HT 1b receptor show increased hyperactivity and impulsivity, with impulsivity being ameliorated when 5-HT 1b receptors are rescued in adulthood (Saudou et al., 1994)[53](Nautiyal et al., 2017). Polymorphisms in 5-HT 1b have also been assessed in transmission disequilibrium and single nucleotide polymorphism (SNP) heritability analysis, along with the 5-HT 2a receptor (Gizer et al., 2009)[55](Quist et al., 2003)(Bidwell et al., 2017)"

"It is of particular note that alterations in serotonergic transmission have also been linked to changes in dopaminergic transmission. It is well observed that dopamine release in several brain regions is modulated by 5-HT receptor activity, and as such it is plausible that changes in dopamine and 5-HT observed in ADHD may indeed be interlinked (Oades et al., 2008)(Yadid et al., 1994)(Boulenguez et al., 1996)."

(Meer et al., 2016)

The interaction between 5-HTTLPR and stress exposure influences connectivity of the executive control and default mode brain networks

"We recently reported that the serotonin transporter polymorphism 5-HTTLPR moderates the relation between stress exposure and attention-deficit/hyperactivity disorder (ADHD) severity. This gene-environment interaction (GxE) has been previously tied to the processing of emotional stimuli, which is increasingly recognized to be a key factor in ADHD-related impairment. The executive control and default mode brain networks play an important role in the regulation of emotion processing, and altered connectivity of these networks has also been associated with ADHD. We therefore investigated whether resting-state connectivity of either of these networks mediates the relation of 5-HTTLPR and stress exposure with ADHD severity. Resting-state functional magnetic resonance imaging, genetic, and stress exposure questionnaire data was available for 425 adolescents and young adults (average age 17.2 years). We found that 5-HTTLPR S-allele carriers showed a more negative relation between stress exposure and connectivity of the executive control network than L-allele homozygotes, specifically in the pre/postcentral gyrus, striatum, and frontal pole. In the default mode network, we found a positive association between the GxE and supramarginal gyrus connectivity. Connectivity of either network did not significantly mediate the effect of this GxE on ADHD. Opposite effects of stress exposure on connectivity in the executive and default mode networks may contribute to findings that stress exposure is associated with lowered cognitive control and heightened levels of rumination and worrying, for S-allele carriers but not L-allele homozygotes. When combined, these effects on connectivity of both networks may relate to the emotional problems seen in individuals with ADHD."

Cholinergic and Other Neurotransmitter Systems

Beyond dopamine and serotonin, ADHD genetics involves cholinergic system variants (particularly CHRNA7 duplications) and noradrenergic genes affecting attention and working memory. The glutamatergic system also shows copy number variants associated with cognitive impairments in ADHD, highlighting the multi-neurotransmitter nature of the disorder. (4 sources)

While dopaminergic and serotonergic systems have received the most attention in ADHD genetics research, several other neurotransmitter pathways contribute significantly to the disorder's genetic architecture. The cholinergic system has emerged as particularly important, with duplications in the CHRNA7 gene at

chromosome 15q13.3 showing consistent associations with ADHD risk (Poddar et al., 2025) (Williams et al., 2012). These CHRNA7 duplications occur in approximately 0.6% of ADHD populations with a relatively large effect size (odds ratio=2.22), and appear to be associated with comorbid conduct disorder (Williams et al., 2012).

The noradrenergic system represents another important pathway in ADHD pathophysiology, with neurobiological and pharmacological studies suggesting that dysregulation of the central noradrenergic system contributes to core ADHD symptoms (Kang et al., 2025). Alpha-2-adrenergic receptors play a major role in working memory and focused attention, as well as deficits in inhibitory control, which are recognized as core deficits of ADHD (Kang et al., 2025). Key genes in this pathway include ADRA2A, which encodes presynaptic inhibitory autoreceptors that regulate norepinephrine release, and SLC6A2, which encodes the transporter responsible for norepinephrine reuptake (Kang et al., 2025).

The glutamatergic system also shows significant involvement in ADHD genetics through copy number variants (CNVs) in glutamate metabotropic receptor genes (Poddar et al., 2025) (Akutagava-Martins et al., 2014). While no significant difference in total CNV burden was found between ADHD and control populations, CNVs in glutamatergic genes were associated with lower IQ scores in ADHD samples and increased anxiety disorders, particularly for CNVs in GRM5 (Akutagava-Martins et al., 2014).

These findings underscore the importance of considering gene-gene interactions and combined effects across multiple neurotransmitter systems, as genetic variants may act synergistically or antagonistically to influence ADHD outcomes (Kang et al., 2025). The polygenic nature of ADHD is evident from genome-wide association studies, with multiple genes involved in neuronal wiring and various neurotransmitter regulations contributing to overall genetic susceptibility (Poddar et al., 2025).

Evidence

(Poddar et al., 2025)

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Genome-Wide Analysis of Copy Number Variants in Attention Deficit Hyperactivity Disorder: The Role of Rare Variants and Duplications at 15q13.3

"Objective: Attention deficit hyperactivity disorder (ADHD) is a common, highly heritable psychiatric disorder. Because of its multifactorial etiology, however, identifying the genes involved has been difficult. The authors followed up on recent findings

suggesting that rare copy number variants (CNVs) may be important for ADHD etiology. Method: The authors performed a genome-wide analysis of large, rare CNVs (<1% population frequency) in children with ADHD (N=896) and comparison subjects (N=2,455) from the IMAGE II Consortium. Results: The authors observed 1,562 individually rare CNVs >100 kb in size, which segregated into 912 independent loci. Overall, the rate of rare CNVs >100 kb was 1.15 times higher in ADHD case subjects relative to comparison subjects, with duplications spanning known genes showing a 1.2-fold enrichment. In accordance with a previous study, rare CNVs >500 kb showed the greatest enrichment (1.28-fold). CNVs identified in ADHD case subjects were significantly enriched for loci implicated in autism and in schizophrenia. Duplications spanning the CHRNA7 gene at chromosome 15q13.3 were associated with ADHD in single-locus analysis. This finding was consistently replicated in an additional 2,242 ADHD case subjects and 8,552 comparison subjects from four independent cohorts from the United Kingdom, the United States, and Canada. Presence of the duplication at 15q13.3 appeared to be associated with comorbid conduct disorder. Conclusions: These findings support the enrichment of large, rare CNVs in ADHD and implicate duplications at 15q13.3 as a novel risk factor for ADHD. With a frequency of 0.6% in the populations investigated and a relatively large effect size (odds ratio=2.22, 95% confidence interval=1.5–3.6), this locus could be an important contributor to ADHD etiology."

(Kang et al., 2025)

The Role of Gene–Gene Interaction Between ADRA2A and SLC6A2 Polymorphisms in Attention System and Treatment Outcomes for Children with ADHD

"The noradrenergic system may also be attractive candidates for the etiology of ADHD [4]. Previous neurobiological and pharmacological studies have suggested that the dysregulation of the central noradrenergic system may be involved in the pathophysiology of ADHD [5,6]. According to Arnsten's hypothesis, alpha-2-adrenergic receptors play a major role in working memory or focused attention, as well as deficits in inhibitory control, which are known as the core deficits of ADHD [7,8]"

"ADRA2A encodes presynaptic inhibitory autoreceptors that regulate norepinephrine release, while SLC6A2 encodes the transporter responsible for norepinephrine reuptake (Berridge et al., 2006)(Davids et al., 2002)(Spencer et al., 2002)(Eiland et al., 2004)"

"Gene variants may affect disease outcomes by acting synergistically or antagonistically; thus, their combined effect is an important aspect of disease etiology [28]."

(Akutagava-Martins et al., 2014)

Glutamatergic copy number variants and their role in attention-deficit/hyperactivity disorder

"Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder with a strong genetic component. The glutamate metabotropic receptor genes (GRMs) have been considered potential candidates for ADHD susceptibility. The aim of the present study was to investigate if copy number variants (CNVs) in GRM1, GRM5, and GRM8 genes are overrepresented in ADHD subjects. A total of 1038 individuals with ADHD and 1057 subjects without this disorder were investigated. No significant difference in the total number of CNVs was found comparing the entire ADHD sample and the population sample without ADHD (P = 0.326, OR = 1.112, 95% CI = 0.762–1.624). The presence of CNVs was associated with lower intelligence quotient (IQ) scores in ADHD samples (P = 0.026, OR = 1.824, 95% CI = 1.066–3.121) but not in the sample of individuals without ADHD. CNVs in GRM5 were associated with presence of anxiety disorders in ADHD cases (P = 0.002, OR = 3.915, 95% CI = 1.631–9.402), but not in individuals without ADHD. Taken together, our results suggest a role for glutamate in ADHD as CNVs in the glutamatergic genes investigated herein were associated with cognitive and clinical characteristics of ADHD individuals. © 2014 The Authors. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics Published by Wiley Periodicals, Inc."

Synaptic Function and Plasticity SNPs

SNAP25 variants are among the most replicated genetic findings in ADHD, being associated in over 70% of studies, and the gene plays crucial roles in both neurotransmitter release and neural network formation. Beyond SNAP25, synaptic plasticity genes affect vesicle fusion, spine morphogenesis, and the establishment of neural circuits that form the physical substrate of memory and learning. (5 sources)

Synaptic function and plasticity genes represent a critical component of ADHD genetics, with SNAP25 emerging as one of the most consistently replicated genetic associations. The SNAP25 gene has shown strong links to ADHD, being associated in over 70% of candidate gene studies, making it one of the most robust genetic findings alongside DRD4 (Poddar et al., 2025) (Taylor et al., 2023).

The SNAP-25 protein plays a fundamental role in synaptic communication through its involvement in synaptic vesicle fusion, a process that is crucial for neurotransmitter release and essential for memory and learning (Huang et al., 2023). SNAP-25 functions as a critical component of the synaptic vesicle fusion machinery that enables fast, calcium-triggered release of neurotransmitters, and it also regulates axonal elongation and specification, suggesting its role in the establishment of neural networks that form the

physical substrate of memory (Huang et al., 2023).

Research has revealed that SNAP25 alterations occur in both ADHD patients and animal models of the disorder, with studies showing innate overexpression of Snap25 protein in ADHD model mice, indicating possible alterations in the SNARE protein complex and potential neurotransmitter dysregulation (Custodio et al., 2025) (Antonucci et al., 2016). The protein's dysfunction may contribute to ADHD through multiple mechanisms, as SNAP-25 not only controls exocytotic and endocytotic processes at the presynaptic terminal but also regulates postsynaptic receptor trafficking, spine morphogenesis, and plasticity (Custodio et al., 2025) (Antonucci et al., 2016).

The involvement of synaptic plasticity genes in ADHD extends beyond individual neurotransmitter systems, as these genes contribute to the overall polygenic architecture of the disorder. Multiple genes involved in neuronal wiring contribute to genetic susceptibility, underscoring that ADHD's genetic basis involves fundamental processes of neural development and synaptic communication rather than isolated neurotransmitter pathway defects (Poddar et al., 2025). This suggests that effective genetic profiling for ADHD must consider variants affecting basic synaptic machinery alongside neurotransmitter-specific pathways.

Evidence

(Poddar et al., 2025)

Unraveling Attention-Deficit/Hyperactivity Disorder Etiology: Current Challenges and Future Directions in Treatment

"ADHD has a strong heritable component, with genetic factors contributing approximately 74% to the overall risk of developing the disorder"

"large-scale genome-wide association studies (GWAS) have identified over 7300 genetic variants that increase risk, underscoring the polygenic nature of ADHD"

"Key genes involved in dopamine regulation, such as DRD4 and DAT1, have emerged as central players in the genetic architecture of ADHD"

"Candidate gene studies have identified significant polymorphisms in genes like SLC6A3 (dopamine transporter) [41], DRD4 and DRD5 (dopamine receptors) (Swanson et al., 1998)[43], SLC6A4 (serotonin transporter), HTR1B (serotonin receptor), and SNAP25 (synaptosome protein). Both DRD4 and SNAP25 have shown strong links to ADHD (Taylor et al., 2023), each being associated in over 70% of studies, while DRD5 and SLC6A3 [43] were associated in 60% of studies"

"the overall effect size of individual variants is small, and much of the genetic risk is believed to arise from the cumulative influence of multiple small-risk variants, as indicated by polygenic risk scores (PRSs)"

"The polygenic nature of ADHD is evident from GWAS findings, as multiple genes, including those involved in dopamine regulation (DUSP6) and neuronal wiring (SEMA6D), contribute to the overall genetic susceptibility [65]"

"duplications in the CHRNA7 gene, which modulates dopaminergic neurons, highlight the importance of glutamatergic and cholinergic pathways in ADHD's pathophysiology (Williams et al., 2012)(Akutagava-Martins et al., 2014)(Mick et al., 2008)(Carrey et al., 2007)."

(Taylor et al., 2023)

A twin study of genetic and environmental contributions to attention-deficit/hyperactivity disorder over time.

"BACKGROUND
Attention-deficit/hyperactivity disorder (ADHD) is an increasingly commonly diagnosed neurodevelopmental condition. One possibility is that this reflects a genuine increase in the prevalence of ADHD due to secular environmental changes, yet this hypothesis remains untested. We therefore investigated whether the genetic and environmental variance underlying ADHD, and traits of ADHD, has changed over time.

METHODS
We identified twins born from 1982 to 2008 from the Swedish Twin Registry (STR). We linked the STR with the Swedish National Patient Register and Prescribed Drug Register to identify diagnoses of ADHD and prescriptions of ADHD medication for these twins. We also utilized data collected from participants in the Child and Adolescent Twin Study in Sweden (CATSS), born from 1992 to

2008. Their parents completed a structured ADHD screening tool, which was used to measure traits of ADHD and assign broad screening diagnoses of ADHD. We used the classical twin design to test whether the degree to which variation in these measures was influenced by genetic and environmental variation changed over time.

RESULTS
We included 22,678 twin pairs from the STR and 15,036 pairs from CATSS. The heritability of ADHD in the STR ranged from 66% to 86% over time, although these fluctuations were not statistically significant. We observed a modest increase in variance in ADHD traits, from 0.98 to 1.09. This was driven by small increases in the underlying genetic and environmental variance, with heritability estimated as 64%-65%. No statistically significant changes in variance in screening diagnoses were observed.

CONCLUSIONS
The relative contribution of genetic and environmental factors to ADHD has remained stable over time, despite its increasing prevalence. Thus, changes in the underlying etiology of ADHD over time are unlikely to explain the increase in ADHD diagnoses."

(Huang et al., 2023)

Effects of the SNAP-25 MnlI variant on hippocampal functional connectivity in children with attention deficit/hyperactivity disorder

"The SNAP-25 gene, encoding the SNAP-25 protein, has been shown to play a significant role in the process of synaptic vesicle fusion. This process is crucial for communication between neurons, which in turn is critical for memory and learning (Jahn et al., 2006)"

"SNAP-25 is a critical component of the synaptic vesicle fusion machinery that enables the fast, calcium-triggered release of neurotransmitters"

"SNAP-25 regulates axonal elongation and specification, suggesting its role in the establishment of neural networks, which form the physical substrate of memory."

(Custodio et al., 2025)

Unraveling Predominantly Inattentive ADHD (ADHD-PI): Insights from Proteomic Analysis of the Striatum of Thyroid Hormone-Responsive Protein (THRSP)–Overexpressing Mice

"Our analysis revealed an innate overexpression of Snap25 protein in THRSP-OE mice, indicating possible alterations in the SNARE protein complex and potential neurotransmitter dysregulation"

"These findings suggest new markers specific to the ADHD-PI presentation and further support the role of Snap25 dysregulation and possible SNARE protein complex alterations in ADHD-PI"

"Snap25 is a protein that plays a key role in regulating neurotransmitter release, and it has been linked to ADHD due to its involvement in dopamine signaling (Antonucci et al., 2016)"

"synaptosomalassociated protein, 25 kDa or Snap25, which is altered in ADHD patients and animal models of ADHD (Brophy et al., 2001)(Zhang et al., 2011)(Wilson, 2000), indicating a relationship between Snap25 and ADHD."

(Antonucci et al., 2016)

SNAP-25, a Known Presynaptic Protein with Emerging Postsynaptic Functions

"A hallmark of synaptic specializations is their dependence on highly organized complexes of proteins that interact with each other. The loss or modification of key synaptic proteins directly affects the properties of such networks, ultimately impacting synaptic function. SNAP-25 is a component of the SNARE complex, which is central to synaptic vesicle exocytosis, and, by directly interacting with different calcium channels subunits, it negatively modulates neuronal voltage-gated calcium channels, thus regulating intracellular calcium dynamics. The SNAP-25 gene has been associated with distinct brain diseases, including Attention Deficit Hyperactivity Disorder (ADHD), schizophrenia and bipolar disorder, indicating that the protein may act as a shared biological substrate among different "synaptopathies". The mechanisms by which alterations in SNAP-25 may concur to these psychiatric diseases are still undefined, although alterations in neurotransmitter release have been indicated as potential causative processes. This review summarizes recent work showing that SNAP-25 not only controls exo/endocytic processes at the presynaptic terminal, but also regulates postsynaptic receptor trafficking, spine morphogenesis, and plasticity, thus opening the possibility that SNAP-25 defects may contribute to psychiatric diseases by impacting not only presynaptic but also postsynaptic functions."

Epigenetic Regulation and Environmental Interactions

DNA methylation patterns at birth can predict later ADHD symptoms, with key genes like VIPR2 showing consistent methylation differences between ADHD cases and controls. Environmental factors interact with genetic variants through

epigenetic mechanisms, particularly affecting dopaminergic pathway genes through processes like methylation, acetylation, and SUMOylation. (8 sources)

Epigenetic mechanisms represent a crucial layer of regulation in ADHD genetics, providing a molecular bridge between genetic susceptibility and environmental influences. Early candidate gene studies investigating DNA methylation primarily targeted genes in the dopaminergic network, including DRD4, but recent epigenome-wide association studies (EWAS) have identified DNA methylation at other genetic loci associated with increased risk for attention problems in children (Camerota et al., 2024) (Wang et al., 2019) (Neumann et al., 2019) (Mooney et al., 2020) (Walton et al., 2016) (Chen et al., 2017) (Goodman et al., 2020).

The VIPR2 gene has emerged as a particularly robust epigenetic marker for ADHD, as methylation of this gene—which codes a receptor for a small neuropeptide with neurotransmitter and neuroendocrine functions—was shown to differentiate between ADHD cases and controls in boys age 7-12, in a sample of twin pairs discordant for ADHD, and in the most recent case-control EWAS of approximately 600 children age 7-12 (Camerota et al., 2024) (Mooney et al., 2020).

Timing appears critical in epigenetic regulation of ADHD, with DNA methylation at birth showing stronger predictive power than school-age methylation patterns. Large-scale studies have identified nine CpGs at birth that predicted later ADHD symptoms, including sites in ERC2 (which regulates neurotransmitter release) and CREB5 (associated with neurite outgrowth), while no CpGs at school age showed comparable associations (Neumann et al., 2019). Additional birth-associated sites include genes involved in neural tube development (SKI), previously implicated in ADHD (ZNF544), intellectual disability (ST3GAL3), and peroxisomal processes important for cortical circuit maturation (PEX2) (Walton et al., 2016).

The dopaminergic pathway shows particular susceptibility to epigenetic regulation, with multiple epigenetic changes including SUMOylation, methylation, and acetylation reported in dopaminergic pathway genes, indicating that this crucial ADHD pathway can be affected by environmental factors and interactions with other neurotransmitter systems (Kessi et al., 2022). Studies of monozygotic twins discordant for ADHD have revealed that epigenetic differences are enriched in genes expressed in brain structures that show anatomical differences between affected and unaffected twins, particularly the striatum and cerebellum, with pathway analyses implicating GABA, dopamine, and serotonin neurotransmitter systems (Chen et al., 2017).

Evidence

(Camerota et al., 2024)

Epigenome-wide association study identifies neonatal DNA methylation associated with two-year attention problems in children born very preterm

> *"Early studies investigating DNA methylation and ADHD consisted of candidate gene studies that primarily targeted genes involved in the dopaminergic network (e.g., DRD4) (Dadds et al., 2016)(Mil et al., 2014)(Xu et al., 2015). In recent years epigenome-wide association studies (EWAS) have reported DNA methylation at other genetic loci associated with increased risk for attention problems in children (Walton et al., 2016)(Neumann et al., 2019)(Mooney et al., 2020)(Wilmot et al., 2016)(Chen et al., 2017)(Wang et al., 2019)(Goodman et al., 2020). Methylation of the VIPR2 gene-a gene that codes a receptor for a small neuropeptide with neurotransmitter and neuroendocrine functions-was shown to differentiate between ADHD cases and controls in boys age 7-12 [16], in a sample of twin pairs discordant for ADHD [17], and in the most recent case-control EWAS of approximately 600 children age 7-12 [15]."*

(Wang et al., 2019)

A powerful and flexible weighted distance-based method incorporating interactions between DNA methylation and environmental factors on health outcomes

> *"MOTIVATION*
> *Deoxyribonucleic acid (DNA) methylation plays a crucial role in human health. Studies have demonstrated associations between DNA methylation and environmental factors with evidence also supporting the idea that DNA methylation may modify the risk of environmental factors on health outcomes. However, due to high dimensionality and low study power, current studies usually focus on finding differential methylation on health outcomes at CpG level or gene level combining multiple CpGs and/or finding environmental effects on health outcomes but ignoring their interactions on health outcomes. Here we introduce the idea of a pseudo-data matrix constructed with cross-product terms between CpGs and environmental factors that are able to capture their*

interactions. We then develop a powerful and flexible weighted distance-based method with the pseudo-data matrix where association strength was used as weights on CpGs, environmental factors and their interactions to up-weight signals and down-weight noises in distance calculations.

RESULTS
We compared the power of this novel approach and several comparison methods in simulated datasets and the Mothers and Newborns birth cohort of the Columbia Center for Children's Environmental Health to determine whether prenatal polycyclic aromatic hydrocarbons interacts with DNA methylation in association with Attention Deficit Hyperactivity Disorder and Mental Development Index at age 3.

AVAILABILITY AND IMPLEMENTATION
An R code for the proposed method Dw-M-E-int together with a tutorial and a sample dataset is available for downloading from http://www.columbia.edu/ sw2206/softwares.htm.

SUPPLEMENTARY INFORMATION
Supplementary data are available at Bioinformatics online."

(Neumann et al., 2019)

Association between DNA methylation and ADHD symptoms from birth to school age: a prospective meta-analysis

"Attention-deficit and hyperactivity disorder (ADHD) is a common childhood disorder with a substantial genetic component. However, the extent to which epigenetic mechanisms play a role in the etiology of the disorder is unknown. We performed epigenome-wide association studies (EWAS) within the Pregnancy And Childhood Epigenetics (PACE) Consortium to identify DNA methylation sites associated with ADHD symptoms at two methylation assessment periods: birth and school age. We examined associations of both DNA methylation in cord blood with repeatedly assessed ADHD symptoms (age 4–15 years) in 2477 children from 5 cohorts and of DNA methylation at school age with concurrent ADHD symptoms (age 7–11 years) in 2374 children from 9 cohorts, with 3 cohorts participating at both timepoints. CpGs identified with nominal significance ($p < 0.05$) in either of the EWAS were correlated between timepoints ($\rho = 0.30$), suggesting overlap in associations; however, top signals were very different. At birth, we identified nine CpGs that predicted later ADHD symptoms ($p < 1 \times 10^{-7}$), including ERC2 and CREB5 . Peripheral blood DNA methylation at one of these CpGs (cg01271805 in the promoter region of ERC2 , which regulates neurotransmitter release) was previously associated with brain methylation. Another (cg25520701) lies within the gene body of CREB5 , which previously was associated with neurite outgrowth and an ADHD diagnosis. In contrast, at school age, no CpGs were associated with ADHD with $p < 1 \times 10^{-7}$. In conclusion, we found evidence in this study that DNA methylation at birth is associated with ADHD. Future studies are needed to confirm the utility of methylation variation as biomarker and its involvement in causal pathways."

(Mooney et al., 2020)

Large epigenome-wide association study of childhood ADHD identifies peripheral DNA methylation associated with disease and polygenic risk burden

"Epigenetic variation in peripheral tissues is being widely studied as a molecular biomarker of complex disease and disease-related exposures. To date, few studies have examined differences in DNA methylation associated with attention-deficit hyperactivity disorder (ADHD). In this study, we profiled genetic and methylomic variation across the genome in saliva samples from children (age 7–12 years) with clinically established ADHD ($N = 391$) and nonpsychiatric controls ($N = 213$). We tested for differentially methylated positions (DMPs) associated with both ADHD diagnosis and ADHD polygenic risk score, by using linear regression models including smoking, medication effects, and other potential confounders in our statistical models. Our results support previously reported associations between ADHD and DNA methylation levels at sites annotated to VIPR2 , and identify several novel disease-associated DMPs ($p < 1e{-}5$), although none of them were genome-wide significant. The two top-ranked, ADHD-associated DMPs (cg17478313 annotated to SLC7A8 and cg21609804 annotated to MARK2) are also significantly associated with nearby SNPs ($p = 1.2e{-}46$ and $p = 2.07e{-}59$), providing evidence that disease-associated DMPs are under genetic control. We also report a genome-wide significant association between ADHD polygenic risk and variable DNA methylation at a site annotated to the promoter of GART and SON ($p = 6.71E{-}8$). Finally, we show that ADHD-associated SNPs colocalize with SNPs associated with methylation levels in saliva. This is the first large-scale study of DNA methylation in children with ADHD. Our results represent novel epigenetic biomarkers for ADHD that may be useful for patient stratification, reinforce the importance of genetic effects on DNA methylation, and provide plausible molecular mechanisms for ADHD risk variants."

(Walton et al., 2016)

Epigenetic profiling of ADHD symptoms trajectories: A prospective, methylome-wide study

"Attention-deficit/hyperactivity disorder (ADHD) is a prevalent developmental disorder, associated with a range of long-term impairments. Variation in DNA methylation, an epigenetic mechanism, is implicated in both neurobiological functioning and psychiatric health. However, the potential role of DNA methylation in ADHD symptoms is currently unclear. In this study, we

examined data from the Avon Longitudinal Study of Parents and Children (ALSPAC)—specifically the subsample forming the Accessible Resource for Integrated Epigenomics Studies (ARIES)—that includes (1) peripheral measures of DNA methylation (Illumina 450k) at birth (n=817, 49% male) and age 7 (n=892, 50% male) and (2) trajectories of ADHD symptoms (7–15 years). We first employed a genome-wide analysis to test whether DNA methylation at birth associates with later ADHD trajectories; and then followed up at age 7 to investigate the stability of associations across early childhood. We found that DNA methylation at birth differentiated ADHD trajectories across multiple genomic locations, including probes annotated to SKI (involved in neural tube development), ZNF544 (previously implicated in ADHD), ST3GAL3 (linked to intellectual disability) and PEX2 (related to perixosomal processes). None of these probes maintained an association with ADHD trajectories at age 7. Findings lend novel insights into the epigenetic landscape of ADHD symptoms, highlighting the potential importance of DNA methylation variation in genes related to neurodevelopmental and peroxisomal processes that play a key role in the maturation and stability of cortical circuits."

(Chen et al., 2017)

Neuroanatomic, epigenetic, and genetic differences in monozygotic twins discordant for Attention Deficit Hyperactivity Disorder

"The study of monozygotic twins discordant for attention deficit hyperactivity disorder can elucidate mechanisms that contribute to the disorder, which affects ~7% of children. First, using in vivo neuroanatomic imaging on 14 pairs of monozygotic twins (mean age 9.7, s.d. 1.9 years), we found that discordance for the disorder is mirrored by differing dimensions of deep brain structures (the striatum and cerebellum), but not the cerebral cortex. Next, using whole-blood DNA from the same twins, we found a significant enrichment of epigenetic differences in genes expressed in these 'discordant' brain structures. Specifically, there is differential methylation of probes lying in the shore and shelf and enhancer regions of striatal and cerebellar genes. Notably, gene sets pertaining to the cerebral cortex (which did not differ in volume between affected and unaffected twins) were not enriched by differentially methylated probes. Genotypic differences between the twin pairs—such as copy number and rare, single-nucleotide variants—did not contribute to phenotypic discordance. Pathway analyses of the genes implicated by the most differentially methylated probes implicated γ-aminobutyric acid (GABA), dopamine and serotonin neurotransmitter systems. The study illustrates how neuroimaging can help guide the search for epigenomic mechanisms in neurodevelopmental disorders."

(Goodman et al., 2020)

Obsessive-compulsive disorder and attention-deficit/hyperactivity disorder: distinct associations with DNA methylation and genetic variation

"Background A growing body of research has demonstrated associations between specific neurodevelopmental disorders and variation in DNA methylation (DNAm), implicating this molecular mark as a possible contributor to the molecular etiology of these disorders and/or as a novel disease biomarker. Furthermore, genetic risk variants of neurodevelopmental disorders have been found to be enriched at loci associated with DNAm patterns, referred to as methylation quantitative trait loci (mQTLs). Methods We conducted two epigenome-wide association studies in individuals with attention-deficit/hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD) (aged 4–18 years) using DNA extracted from saliva. DNAm data generated on the Illumina Human Methylation 450 K array were used to examine the interaction between genetic variation and DNAm patterns associated with these disorders. Results Using linear regression followed by principal component analysis, individuals with the most endorsed symptoms of ADHD or OCD were found to have significantly more distinct DNAm patterns from controls, as compared to all cases. This suggested that the phenotypic heterogeneity of these disorders is reflected in altered DNAm at specific sites. Further investigations of the DNAm sites associated with each disorder revealed that despite little overlap of these DNAm sites across the two disorders, both disorders were significantly enriched for mQTLs within our sample. Conclusions Our DNAm data provide insights into the regulatory changes associated with genetic variation, highlighting their potential utility both in directing GWAS and in elucidating the pathophysiology of neurodevelopmental disorders."

(Kessi et al., 2022)

Attention-deficit/hyperactive disorder updates

"Several genes have been reported to associate with ADHD: DRD1, DRD2, DRD4, DAT1, TPH2, HTR1A, HTR1B, SLC6A4, HTR2A, DBH, NET1, ADRA2A, ADRA2C, CHRNA4, CHRNA7, GAD1, GRM1, GRM5, GRM7, GRM8, TARBP1, ADGRL3, FGF1, MAOA, BDNF, SNAP25, STX1A, ATXN7, and SORCS2"

"The majority of the available animal models are related to the dopaminergic pathway. Epigenetic changes including SUMOylation, methylation, and acetylation have been reported in genes related to the dopaminergic pathway"

"The dopaminergic pathway remains to be crucial in the pathogenesis of ADHD. It can be affected by environmental factors and other pathways."

Gene-Gene Interactions and Polygenic Effects

ADHD's genetic complexity involves over 7,300 variants working together, with individual genes having small effects that combine through polygenic risk scores. Gene-gene interactions occur both within and across neurotransmitter systems, with treatment responses depending on combinations of variants in dopamine, norepinephrine, and metabolic pathways. (5

sources)

The polygenic nature of ADHD is evident from large-scale genome-wide association studies, which have identified over 7,300 genetic variants that increase risk, with the overall effect size of individual variants being small and much of the genetic risk arising from the cumulative influence of multiple small-risk variants, as indicated by polygenic risk scores (Poddar et al., 2025). Multiple genes, including those involved in dopamine regulation (DUSP6) and neuronal wiring (SEMA6D), contribute to the overall genetic susceptibility, underscoring the complex genetic architecture of the disorder (Poddar et al., 2025).

Gene variants may affect disease outcomes by acting synergistically or antagonistically, making their combined effect an important aspect of disease etiology (Kang et al., 2025). This complexity is particularly evident in treatment response, where ADHD medication responses are regulated by genes across multiple pathways including the dopamine pathway (DRD4, SLC6A3), norepinephrine pathway (SLC6A2, ADRA2A), catecholamine metabolism (COMT), and cytochrome P450 isoenzymes including CYP2D6 and CES1 (Zhao et al., 2025).

Recent GWAS findings have revealed novel gene interactions, with significant loci implicating genes like TMEM117 and MYO5B that are associated with both brain- and gut-related disorders, while NKAIN2, an ADHD-related gene also associated with metabolic processes, contributed most to predictive models (Zhao et al., 2025). Cross-disorder genetic overlap is substantial, with genes encoding glutamate and GABA receptors and transporters implicated in multiple neuropsychiatric conditions including ADHD and autism spectrum disorder, supporting a common genetic basis (Grigore et al., 2025) (Naaijen et al., 2017).

The genetic architecture extends beyond traditional neurotransmitter pathways to include genes involved in synaptic plasticity and glutamatergic signaling, which show associations with both ADHD and other psychiatric disorders, as well as metabolic conditions like obesity (Grigore et al., 2025). This broad genetic overlap suggests that effective multi-SNP profiling must account for polygenic effects across diverse biological systems rather than focusing on individual high-effect variants within single pathways.

Evidence

(Poddar et al., 2025)

Unraveling Attention-Deficit/Hyperactivity Disorder Etiology: Current Challenges and Future Directions in Treatment

> *"ADHD has a strong heritable component, with genetic factors contributing approximately 74% to the overall risk of developing the disorder"*
>
> *"large-scale genome-wide association studies (GWAS) have identified over 7300 genetic variants that increase risk, underscoring the polygenic nature of ADHD"*
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> *"Key genes involved in dopamine regulation, such as DRD4 and DAT1, have emerged as central players in the genetic architecture of ADHD"*
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> *"Candidate gene studies have identified significant polymorphisms in genes like SLC6A3 (dopamine transporter) [41], DRD4 and DRD5 (dopamine receptors) (Swanson et al., 1998)[43], SLC6A4 (serotonin transporter), HTR1B (serotonin receptor), and SNAP25 (synaptosome protein). Both DRD4 and SNAP25 have shown strong links to ADHD (Taylor et al., 2023), each being associated in over 70% of studies, while DRD5 and SLC6A3 [43] were associated in 60% of studies"*
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> *"duplications in the CHRNA7 gene, which modulates dopaminergic neurons, highlight the importance of glutamatergic and cholinergic pathways in ADHD's pathophysiology (Williams et al., 2012)(Akutagava-Martins et al., 2014)(Mick et al., 2008)(Carrey et al., 2007)."*

(Kang et al., 2025)

The Role of Gene–Gene Interaction Between ADRA2A and SLC6A2 Polymorphisms in Attention System and Treatment Outcomes for Children with ADHD

"The noradrenergic system may also be attractive candidates for the etiology of ADHD [4]. Previous neurobiological and pharmacological studies have suggested that the dysregulation of the central noradrenergic system may be involved in the pathophysiology of ADHD [5,6]. According to Arnsten's hypothesis, alpha-2-adrenergic receptors play a major role in working memory or focused attention, as well as deficits in inhibitory control, which are known as the core deficits of ADHD [7,8]"

"ADRA2A encodes presynaptic inhibitory autoreceptors that regulate norepinephrine release, while SLC6A2 encodes the transporter responsible for norepinephrine reuptake (Berridge et al., 2006)(Davids et al., 2002)(Spencer et al., 2002)(Eiland et al., 2004)"

"Gene variants may affect disease outcomes by acting synergistically or antagonistically; thus, their combined effect is an important aspect of disease etiology [28]."

(Zhao et al., 2025)

Genome data based deep learning identified new genes predicting pharmacological treatment response of attention deficit hyperactivity disorder

"The current GWAS results identified two significant loci (rs10880574, P = 2.39E-09; rs2000900, P = 3.31E-09) which implicated two genes, TMEM117 and MYO5B, that were primarily associated with both brain- and gut-related disorders"

"Notably, the variant that contributed most to the CNN model was NKAIN2, an ADHD-related gene, which is also associated with metabolic processes"

"Previous candidate gene-based studies showed that ADHD treatment responses were probably regulated by genes involved in neurotransmitter system (Myer et al., 2018), including dopamine pathway (DRD4, SLC6A3), norepinephrine pathway (SLC6A2, ADRA2A), and catecholamines metabolism (COMT); and cytochrome P450 isoenzyme [8](Trzepacz et al., 2008), including CYP2D6 and CES1."

(Grigore et al., 2025)

Recent Advances in the Etiology and Neural Pathways Underlying Attention-Deficit and Hyperactivity Disorder

"Variations in genes related to dopamine regulation, such as the DRD4 and DRD2 genes, have been associated with ADHD. These genetic differences may affect neurotransmitter pathways, influencing attention and behavior regulation"

"Genetic investigations have identified several candidate genes implicated in ADHD, particularly within the dopaminergic system, including DRD1, DRD2, DRD4, and DAT1 [64]. Additionally, serotonergic pathway genes such as SLC6A4 and glutamatergic system genes including GRIN2B have also been associated with ADHD susceptibility [61]"

"Furthermore, genes encoding glutamate and GABA receptors and transporters have been implicated in multiple neuropsychiatric conditions, including ADHD and autism spectrum disorder, further supporting a common genetic basis (Naaijen et al., 2017)"

"Further research has highlighted the role of central nervous system pathways in obesity, with meta-analyses revealing associations between obesity and genes involved in synaptic plasticity and glutamatergic signaling, which are also implicated in ADHD and other psychiatric disorders [68]."

(Naaijen et al., 2017)

Glutamatergic and GABAergic gene sets in attention-deficit/hyperactivity disorder: association to overlapping traits in ADHD and autism

"Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) often co-occur. Both are highly heritable; however, it has been difficult to discover genetic risk variants. Glutamate and GABA are main excitatory and inhibitory neurotransmitters in the brain; their balance is essential for proper brain development and functioning. In this study we investigated the role of glutamate and GABA genetics in ADHD severity, autism symptom severity and inhibitory performance, based on gene set analysis, an approach to investigate multiple genetic variants simultaneously. Common variants within glutamatergic and GABAergic genes were investigated using the MAGMA software in an ADHD case-only sample (n=931), in which we assessed ASD symptoms and response inhibition on a Stop task. Gene set analysis for ADHD symptom severity, divided into inattention and hyperactivity/impulsivity symptoms, autism symptom severity and inhibition were performed using principal component regression analyses. Subsequently, gene-wide association analyses were performed. The glutamate gene set showed an association with severity of hyperactivity/impulsivity (P=0.009), which was robust to correcting for genome-wide association levels. The GABA gene set showed nominally significant association with inhibition (P=0.04), but this did not survive correction for multiple comparisons. None of single gene or single variant associations was significant on their own. By analyzing multiple genetic variants within candidate gene sets together, we were able to find genetic associations supporting the involvement of excitatory and inhibitory neurotransmitter systems in ADHD and ASD symptom severity in ADHD."

Applications for Multi-SNP Profiling

Multi-SNP profiling for ADHD can improve personalized medicine by predicting treatment responses and identifying individuals at high genetic risk, but current polygenic risk scores explain only a small portion of ADHD heritability and require larger, more diverse datasets to become clinically useful. (LLM Memory)

The development of multi-SNP profiling approaches for ADHD holds significant promise for personalized medicine applications, though current limitations must be addressed before widespread clinical implementation. Polygenic risk scores (PRS) represent the most advanced application of multi-SNP profiling, combining information from thousands of genetic variants to estimate individual ADHD risk (Model-Generated). However, current PRS models explain only 10-28% of ADHD heritability despite the disorder's 60-90% heritability from twin studies, indicating substantial room for improvement (Model-Generated).

Treatment response prediction represents one of the most clinically relevant applications of multi-SNP profiling. Since ADHD medication responses are regulated by genes across multiple pathways including dopamine (DRD4, SLC6A3), norepinephrine (SLC6A2, ADRA2A), catecholamine metabolism (COMT), and drug metabolism enzymes (CYP2D6, CES1), comprehensive genetic profiles could help clinicians select optimal medications and dosing strategies for individual patients (Model-Generated). This pharmacogenomic approach could reduce the current trial-and-error process of ADHD treatment and minimize adverse effects.

Risk stratification for early intervention represents another promising application, particularly given that DNA methylation patterns at birth can predict later ADHD symptoms more accurately than school-age patterns (Model-Generated). Multi-SNP profiles combined with epigenetic markers could identify high-risk children before symptom onset, enabling targeted prevention strategies and early monitoring. The identification of genes like VIPR2, which show consistent methylation differences between ADHD cases and controls, suggests that combining genetic variants with epigenetic markers could improve predictive accuracy (Model-Generated).

For advocacy and policy applications, multi-SNP profiling can provide objective evidence of ADHD's biological basis, potentially reducing stigma and supporting accommodation requests in educational and workplace settings. The demonstration that over 7,300 genetic variants contribute to ADHD risk provides compelling evidence that the disorder has a strong biological foundation rather than being solely behavioral or environmental (Model-Generated). However, ethical considerations around genetic testing, privacy, and potential discrimination must be carefully addressed as these technologies advance toward clinical implementation.